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(54) Title: RACEMISATION PROCESS FOR USE IN THE MANUFACTURE OF LEVOBUPIVACAINE AND RELATED PIPERIDINECARBOXANILIDE ANAESTHETIC AGENTS

(57) Abstract

An optically-enriched piperidine-2-carboxanilide compound, in which the piperidine is optionally N-alkylated, is racemised by heating the compound in an aqueous medium, provided that the medium includes an organic cosolvent if the compound is N-alkylated. This process is particularly valuable, in conjuction with a resolution process, for the manufacture of levobupivacaine.

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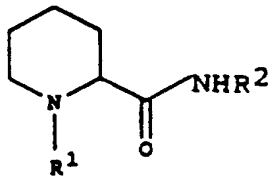
RACEMISATION PROCESS FOR USE IN THE MANUFACTURE OF LEVOBUPIVACAINE AND RELATED PIPERIDINECARBOXANILIDE ANAESTHETIC AGENTS

Field of the Invention

This invention relates to the racemisation of optically-enriched piperidine-2-carboxanilides. In particular, the process is suitable for use in the manufacture of levobupivacaine and related piperidinecarboxanilide anaesthetic agents.

Background to the Invention

Compounds of formula 1



wherein R^2 is 2,6-dimethylphenyl and R^1 is methyl (mepivacaine), *n*-propyl (ropivacaine as S-enantiomer) or *n*-butyl (bupivacaine) are widely used as local anaesthetics. The corresponding compound when R^1 is H is a useful intermediate.

Biological studies have shown that the (*S*)-enantiomers of such N-alkyl-piperidine-2-carboxanilides display lower cardiotoxicity than the corresponding racemates, whilst maintaining the same anaesthetic potency, and are therefore more beneficial for clinical uses. Thus there is a requirement for efficient processes to manufacture compounds of formula 1 in the form of single enantiomers. For this purpose, conventional resolution approaches invariably afford up to 50% of the unwanted enantiomer. To improve atom utilisation in such processes, it is desirable to recycle the unwanted enantiomer by effecting its racemisation in order to provide material suitable for subsequent resolution.

Friberger *et al*, Acta. Pharm. Suec. (1971) 8:361-364, report a study of the solubility and partition coefficients of the racemates and enantiomers of mepivacaine and bupivacaine. It is reported that racemic bupivacaine is more soluble than the isomers at a pH above 6. All of the compounds tested have solubilities decreasing to low levels, especially for bupivacaine, at pH values approaching neutrality.

Fyhr *et al*, Acta.Pharm.Suec. (1988) 25:121-132, report the racemisation of optically-enriched ropivacaine hydrochloride in dilute aqueous solution at pH 1-6 and 80-130°C. HCl or citric acid was present, in order to establish the pH. The conclusions of this pre-formulation stability study were that the racemisation involves hydroxyl ion-catalysed racemisation of the *N*-protonated species. This study provides no useful indication as to how to conduct racemisation as such, and does not suggest any volume-efficient commercial process.

Summary of the Invention

The present invention is based on the surprising discovery that piperidine-2-carboxanilides, including compounds of formula 1 wherein R^1 is H, methyl, *n*-propyl or *n*-butyl and R^2 is 2,6-dimethylphenyl, undergo rapid racemisation when heated in aqueous solution, provided that an organic cosolvent is present when R^1 is not H. The practical nature of this discovery is evident in that much more concentrated systems can be used than in the prior art.

Whereas, at concentrations of 30 mg/ml, at a pH above 5, the use of conditions otherwise specified by Fyhr *et al* lead to complete inhibition of racemisation of ropivacaine and bupivacaine, the rate of racemisation can be increased, under the conditions used in this invention, with increasing pH of the solution. Racemisation occurs most efficiently at a pH greater than 6, without loss of solubility, which means that no acid need be added.

Description of the Invention

The reaction can be carried out in water alone, when R^1 is H. In this case, a preferred embodiment of the invention is the racemisation of optically-enriched 2',6'-dimethylpiperidine-2-carboxanilide (1: R^1 = H, R^2 = 2,6-dimethylphenyl).

Alternatively, for N-alkylpiperidine compounds of formula 1, the reaction is carried out in the presence of an organic cosolvent such as an alcohol or polyol, e.g. ethylene glycol thus allowing solutions of higher concentration to be used, than in the prior art. A preferred embodiment of this aspect of the invention is the racemisation of optically-enriched bupivacaine in ethylene glycol containing 10% v/v water. The presence of salt forms of compounds of formula 1 does not impede the efficiency of the racemisation process.

The reaction conditions may comprise heating, as desired. Suitable conditions will depend on the nature of the reactants, but can be readily chosen by those skilled in the art.

In summary, the present invention establishes simple and economical processes for the racemisation of piperidine-2-carboxanilides, in either neat aqueous media or aqueous media combined with inert organic cosolvents. The invention is particularly suited to the optimum utilisation of unwanted enantiomer in the preparation of enantiopure therapeutic agents, and therefore in practice the starting material will usually be richer in the (*R*)-enantiomer. When R^1 is H, a compound of formula 1 is an intermediate *en route* to anaesthetic agents. When R^1 is n-butyl, the present invention is of particular utility for preparing (*S*)-bupivacaine, in conjunction with a resolution process, e.g. that described in PCT/GB95/02513 and South African Application No. 95/8993.

The following Examples illustrate the invention.

Example 1

(*S*)-2',6'-Dimethylpiperidine-2-carboxanilide (>99% ee, 155 mg, 0.67 mmol) was dissolved in water (14.5 ml). The pH was measured to be 9.97. The solution was heated under reflux for 19 hours. Aqueous ammonia (28% w/v; 1 ml) was added to the cooled solution and the mixture extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried with magnesium sulphate and the solvent removed under reduced pressure to give a white crystalline solid (128 mg). Analysis by chiral HPLC showed this to be racemic 2',6'-dimethylpiperidine-2-carboxanilide.

Example 2

A mixture of (*S*)-bupivacaine (>99% ee, 1.5 g mmol), ethylene glycol (13.5 ml) and water (1.5 ml) was heated at 138°C for 9 hours. On cooling to ambient temperature crystallisation of a solid occurred. The solid was filtered to give a quantitative yield of bupivacaine which was shown by chiral HPLC analysis to be a 52:48 mixture of (*S*)-bupivacaine and (*R*)-bupivacaine.

Example 3

(*S*)-Bupivacaine (>99% ee, 0.27 g, 0.94 mmol) and (*S*)-bupivacaine (-)-tartrate (2:1 salt, 0.23 g, 0.32 mmol) were heated at 150 °C in propan-2-ol (2.5 ml) and water (2.5 ml) in a sealed vessel for 22 hours. A portion of solution was removed, basified with 28% aqueous ammonia and extracted into heptane. The organic solution was dried with magnesium sulphate and the solvent removed under reduced pressure. The residue was shown by chiral HPLC to be a 63:37 mixture of (*S*)-bupivacaine and (*R*)-bupivacaine.

CLAIMS

1. A process for the racemisation of an optically-enriched piperidine-2-carboxanilide compound, in which the piperidine is optionally N-alkylated, which comprises heating the compound in an aqueous medium, provided that the medium includes an organic cosolvent if the compound is N-alkylated.

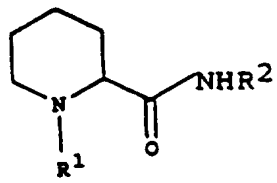
2. A process according to claim 1, wherein a salt form of the compound is also present.

3. A process according to either preceding claim, which is conducted at a pH above 6.

4. A process according to any preceding claim, which is conducted in the absence of added acid.

5. A process according to any preceding claim, where said compound is enriched in the (*R*)-enantiomer.

6. A process according to any preceding claim, wherein the compound is of the formula



wherein R^1 is H or a substituent of up to 20 C atoms and R^2 is C_{6-20} aryl.

7. A process according to claim 6, wherein R^1 is H or C_{1-6} alkyl and R^2 is phenyl optionally substituted with one or more C_{1-4} alkyl groups.

8. A process according to claim 7, wherein R^2 is 2,6-dimethylphenyl.

9. A process according to any preceding claim, wherein the medium comprises water and an organic cosolvent.

10. A process according to claim 9, wherein the cosolvent is an alcohol or polyol.

11. A process according to claim 9, wherein the cosolvent is an ethylene glycol.

12. A process according to claim 8, or to any of claims 9 to 11 when appendant to claim 8, wherein R^1 is n-butyl, for preparing bupivacaine of diminished optical purity.

13. A process according to claim 8, or to any of claims 9 to 11 when appendant to claim 8, wherein R^1 is n-propyl.

14. A process according to claim 8, wherein R^1 is H, for the racemisation of 2',6'-dimethylpiperidine-2-carboxanilide.

15. A process according to any of claims 6, 7, 8 and 14, wherein R^1 is H and the medium consists essentially only of water.

16. A process for preparing (*S*)-bupivacaine, which comprises resolving a mixture of enantiomers of bupivacaine, separating (*S*)-bupivacaine, and racemising residual (*R*)-bupivacaine by a process according to claim 12, prior to further resolution.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 96/00067

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ACTA PHARMACEUTICA SUECICA, vol. 25, no. 3, 1988 pages 121-132, P. FYHR, C. HOGSTROEM 'A Preformulation Study on the Kinetics of the Racemisation of Ropivacaine Hydrochloride' cited in the application see top paragraph on page 131 ---	1-16
A	J. ORG. CHEM., vol. 48, 1983 pages 843-846, S. YAMADA ET. AL. 'Method for the Racemisation of Optically Active Amino Acids' see the whole document --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. ORG. CHEM., vol. 43, no. 1, 6 January 1978 pages 1-5, G.G. SMITH ET. AL. 'Factors Affecting the Rate of Racemisation of Amino Acids and Their Significance to Geochronology' page 2, right column, top paragraph: "Buffer and pH" ---	1-16
X	FR,A,2 301 498 (MAGGIONI & C.) 17 September 1976 see the whole document ---	1-16
A	BULL. CHEM. SOC. JPN., vol. 64, 1991 pages 3251-3255, T. SHIRAIWA ET. AL. 'Asymmetric Transformation of Proline and 2-Piperidinecarboxylic Acid via Formation of Salts with Optically Active Tartaric Acid' see the whole document ---	1-16
A	CHEM. PHARM. BULL., vol. 18, no. 9, September 1970 pages 1794-1798, M. SATO ET. AL. 'Studies on the Racemisation of Amino Acids and Their Derivatives' see the whole document -----	1-16

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Information on patent family members

Int onal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2301498	17-09-76	NONE	